If the brain were so simple we could understand it, we would be so simple we couldn't.
Lyall Watson, philosopher

NEUROLOGY

Marine Toxin Hinders Cognitive Development

Domoic acid, a naturally occurring marine toxin, causes acute symptoms of diarrhea, vomiting, seizures, and memory loss in people sickened by eating contaminated shellfish. Now a recent study reveals that exposure to even tiny amounts of domoic acid *in utero* may produce subtle, long-term cognitive impairment in rats. The new findings raise the possibility that pregnant women who inadvertently eat shellfish tainted with low levels of domoic acid may put their unborn children at risk for lifelong behavioral consequences, says Edward D. Levin, a professor of psychiatry at Duke University Medical Center in Durham, North Carolina. Levin coauthored the study, which is described in the September/October 2005 issue of *Neurotoxicology and Teratology*.

Harmful algal blooms that produce domoic acid are increasing, possibly due to warming ocean waters and human impacts such as farm and sewage runoff. Shellfish take in the toxin when they filter water and incorporate it into their tissues. Along the Florida coast, pigments in the "red tides" caused by *Karenia brevis* and other dinoflagellates signal toxic blooms. However, no distinctive color characterizes toxic blooms elsewhere, such as those along the Oregon coast caused by *Pseudonitzschia*, a phytoplankton that generates domoic acid. "The first warning sign we get for these toxic blooms is when domoic acid shows up in routine testing of shellfish," says Peter Strutton, a biological oceanographer at Oregon State University in Corvallis. Thus, it's possible that shellfish with potentially dangerous levels of domoic acid are being harvested and consumed (Strutton notes that, in Oregon at least, most of the shellfish of concern are those that people catch recreationally on their own).

In the Levin study, the researchers injected pregnant rats with single doses of 0.3, 0.6, or 1.2 milligrams of domoic acid per kilogram body weight at the end of the second trimester. The highest dose was in the low end of the range known to cause acute illness in rats.

During adolescence and adulthood, the offspring underwent a battery of behavioral tests. In a radial-arm maze, which looks like a wagon wheel without its rim, the rats searched for sugary cereal at the ends of arms extending from a central hub. Once eaten, the cereal is not replaced, and the rats must remember which arms they've already explored. This test therefore measures working memory. The females performed the same regardless of dose, while the males performed progressively worse as the dose increased (male rats normally perform better than females in this maze).

Next Levin gave the rats low doses of scopolamine, a drug that causes amnesia and memory impairment. Slightly stressing the brain with a low dose of scopolamine helped to uncover subtle neurological defects caused by domoic acid. Compared to controls, rats exposed to domoic acid had greater memory loss following administration of scopolamine, with the highest-dose group performing the worst. "Animals can normally deal with a low dose of scopolamine," says Levin, "unless there's prior neurotoxic damage that adversely affects the brain."

Now researchers wonder whether domoic acid may negatively affect unborn children even at levels that do not cause symptoms in expectant mothers. The U.S. Food and Drug Administration based its current limits for domoic acid in shellfish on levels that are assumed to be safe for adults. "We may need to re-evaluate the monitoring of waters and seafood to make sure that the most sensitive members of the population are protected from toxic exposure to domoic acid," says Levin. However, he adds, it's important to ensure that fisherman are not unnecessarily cut off from their livelihood and that people are not deprived of the nutritional benefits of uncontaminated seafood.

Strutton and Michelle Wood at the University of Oregon in Eugene are developing a new tool to improve early surveillance of toxic blooms. They are combining satellite data on physical attributes of the ocean such as water color and surface temperature to identify early markers for toxic blooms. In collaboration with the National Oceanic and Atmospheric Administration's CoastWatch program, they plan to develop products for coastal managers such as charts of conditions that raise the risk of domoic acid poisoning of shellfish. CoastWatch also plans to post satellite maps of regions where blooms exist or are developing on its website. "It will warn [managers] to ramp up their shoreline sampling of shellfish beds," Strutton says. **–Carol Potera**

A meal for mothers to skip? New studies in rats show that the marine toxin domoic acid may impair fetal cognitive development when mothers consume contaminated shellfish.

Photodisc

POLICY

Cloud Banks: Airlines Save Halon

The airlines of the developing world are being advised by the United Nations Environment Programme (UNEP) to bank their stocks of halons—chemicals vital for extinguishing aircraft fires—as the 2010 deadline to cease production approaches. Most developed nations already have plans for halon recycling and banking systems—registries of who has excess halon to sell. For developing countries, however, the challenges of starting up such systems may leave some airlines grounded.

Halons have been used for years in many kinds of fire-extinguishing systems. However, when they escape into the atmosphere, UV light causes them to release highly reactive bromine radicals that deplete the ozone layer. Indeed, halons are thought to be three to ten times more ozone-unfriendly than chlorofluorocarbons. For this reason the Montréal Protocol obliged developed nations to cease halon production in 1994, and set a 2010 target date for the developing world.

Fear of firing. Halon, used to put out fires on aircraft, is being phased out with no suitable replacement in sight.

The trouble is that, while replacements for halons now exist for nearly all other applications, these chemicals remain essential for aircraft safety. Jim Curlin, information manager of the UNEP Division of Technology Industry and Economics, OzonAction Branch, explains, "Aircraft fire-extinguishing systems must have good dispersion and fire-suppression functions, must work at low temperatures, be of low toxicity to humans for the time that they are trapped in an affected plane and have an excellent weight-to-volume ratio." Currently, he says, there is no drop-in replacement for halons that has all these characteristics, making halon availability critical to airlines.

Even developed countries are not without halon banking problems. Developed nations have enough halon 1301—which is used in cargo bay and engine fire-fighting equipment—to last some 25 years, by which time a replacement should be available, explains John O'Sullivan, a member of the UNEP Halons Technical Options Committee and fire representative for the International Air Transport Association in Montréal. But there isn't enough halon 1211, which is used by aircrew in handheld extinguishers. "[Halon 1211] can still be made in developing countries, so at least in this respect [developing nations] should have fewer problems," says O'Sullivan. "But European regulations, for example, make it difficult to import. This is a problem we still have to address."

Starting up halon banking systems is certainly in the best interest of developing world airlines. With passenger safety a top priority, aircraft that do not maintain their halon-based systems would eventually fail airworthiness inspections and be banned from flying to many destinations. But how easy will it be for developing countries to start such systems, and where does halon banking figure on their priority list?

"Most focus first on economic problems and then on the environment," says Wilman Rajiman, the Indonesia Halon Bank Project manager at Soekarno-Hatta International Airport in Jakarta. "In Indonesia we started to discuss a national halon bank in 1995, but due to an economic crisis in 1998 it was not launched until March 2000. The major problems we faced were capital investment, knowledge, training, and local regulations."

For many countries, cash flow will be the major obstacle. Rajiman explains that Indonesia received a grant from the World Bank, but must spend its own money and then ask for reimbursement. Poorer nations may find that stipulation difficult, yet airline-servicing companies worldwide must comply strictly with the halon specifications laid down by aircraft manufacturers and foreign aviation authorities. Maintaining proper halon stocks is therefore vital to their business.

Flyers may be comforted to know that the Montréal Protocol contains a clause that allows developing nations to temporarily restart halon production for critical systems if supplies fail—always supposing the necessary infrastructure exists. "That's a situation we all want to avoid," says Curlin, "and one of the reasons we are encouraging companies and countries to develop halon banks."

–Adrian Burton

Top to bottom: Chris Reuther/EHP; Furlong Photography/Alamy; Shutterstock

Back-Door Cigarette Marketing?

At a time when marketing restrictions make it harder for tobacco manufacturers to reach the youth market, a number of new candy- and liqueur-flavored tobacco products are hitting the market. A review of internal tobacco industry documents published in the November/December 2005 issue of *Health Affairs* showed that the industry has long sought to target youth through new flavors, with one document stating that young people's interest in unusual flavors "may indicate new opportunities for enhanced-flavor tobacco products that could leverage [brand's] current strength among younger adult smokers." The authors write that flavored cigarettes can promote youth smoking initiation and help young occasional smokers become daily smokers by reducing or masking the unpleasant taste of tobacco smoke. The authors add there is little information on the potential health effects of the flavorings themselves.

In My Skin

Rates of melanoma, the deadliest skin cancer, continue to climb, more than tripling in Caucasians between 1980 and 2002, according to the American Cancer Society. Now skin cancer experts at the University of Newcastle upon Tyne have developed a novel test that uses a small skin sample and responses to a ten-page questionnaire to produce highly personalized assessments of the risks individuals face from their sun exposure to date. Patients also receive personalized skin protection advice and can re-take the test to see how changes they've made have affected their skin cancer risk. The "skinphysical" test was launched at British clinics in the autumn of 2005.

The Healing Quiet

A new study from The Johns Hopkins University shows that a noisy hospital environment may make patients sicker and lead to higher stress levels and burnout among staff. The study, presented at the 2005 annual meeting of the Acoustical Society of America, found that hospital noise levels worldwide have grown steadily over the past five decades and now on average exceed WHO hospital noise guidelines. This disturbs those within the hospital's confines, raises the risk of medical errors, and can even slow the pace of healing and contribute to lapses in short-term memory. Two possible solutions are to equip hospital personnel with hands-free personal communicators (eliminating the need for loudspeakers) and to wrap fiberglass insulation with an antibacterial fabric to form a sound-absorbent tile for ceilings and walls.

PARKINSON DISEASE

PD Gene and Oxidative Stress

A gene linked to familial Parkinson disease (PD) may protect neurons from oxidative damage, according to two independent studies in the fruit fly *Drosophila*. Flies lacking the *DJ-1* gene showed selective sensitivity to widely used agricultural toxicants that kill neurons mainly through oxidative stress. The studies, published 6 September 2005 in *Current Biology*, suggest that normally "*DJ-1* has a neuroprotective role against different oxidative stimuli," says Darren Moore, an instructor in neurology at the Johns Hopkins University School of Medicine who has studied the gene. However, if *DJ-1* stops working—because of either an inherited mutation or toxicant exposure—oxidative stress may wreak havoc on the brain, killing dopamine-producing neurons.

Experiments in cultured cells and in knockout mice have hinted that *DJ-1* mutations may sensitize cells to the harmful effects of oxidative stress. This type of oxidative damage happens when unstable oxygen molecules react with certain components inside cells in a manner similar to the process that converts iron to rust. Many environmental insults—including exposure to certain agricultural chemicals—can generate these unstable oxygen molecules.

To pin down how *DJ-1* interacts with such oxidative stress agents, Nancy Bonini, a professor of biology at the University of Pennsylvania, Philadelphia, and her colleagues first identified *DJ-1* in *Drosophila*, which they found exists in two forms: *DJ-1*α (expressed primarily in the testes) and *DJ-1*β (expressed everywhere). They then created a line of *Drosophila* mutants completely lacking both forms.

The flies with no *DJ-1* had normal life spans and showed no neuronal degeneration. However, when Bonini and her colleagues exposed flies to the herbicide paraquat, *DJ-1* mutants died much sooner than normal flies. The mutants also showed marked sensitivity to the insecticide rotenone and to hydrogen peroxide—both agents that promote oxidative stress. These results suggest that *DJ-1* normally protects against oxidative stress and that its inactivation may leave neurons susceptible to oxidative damage. The team also found that exposure to paraquat led to biochemical modification of the DJ-1β protein, a change Bonini says may somehow influence the ability of *DJ-1* to protect neurons from oxidative damage.

In the other paper, Kyung-Tai Min, an investigator at the National Institute of Neurological Disorders and Stroke, and his colleagues examined a different type of *Drosophila DJ-1* mutant. They disrupted the function of *DJ-1*β by inserting a mutation into the middle of the gene. Surprisingly, Min says, they found that dopaminergic neurons in these mutants survived longer into old age than did neurons of normal flies. They also found that their *DJ-1*β mutants were much more resistant to paraquat insult than were normal flies.

Further examination revealed that these flies had elevated *DJ-1*α expression—the loss of *DJ-1*β somehow encouraged a compensatory upregulation of *DJ-1*α, which the authors believe protected the fly from paraquat-induced oxidative damage. When they treated the same flies with hydrogen peroxide, however, they found that the *DJ-1*β mutants were extremely susceptible to early death. Min says this suggests that *DJ-1*α and *DJ-1*β may normally protect cells against different types of agents that promote oxidative stress.

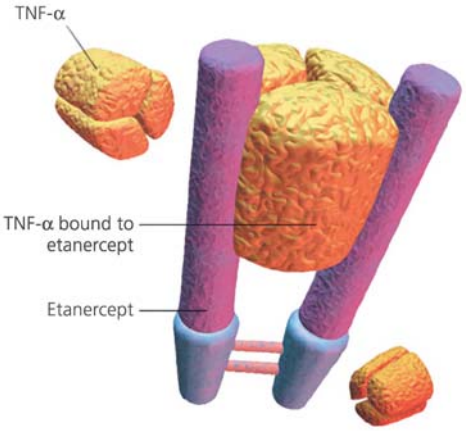
Neither of the mutant *DJ-1* fly strains will probably make an ideal model for PD, according to Moore, because the flies don't suffer from the neurodegeneration seen in humans with *DJ-1* mutations. Nevertheless, says Bonini, studies of *DJ-1* in *Drosophila* will provide greater understanding of fundamental activities of the gene, helping to elucidate how its function may be critical in PD. **–Melissa Lee Phillips**

ASTHMA

Expanding the Medicine Chest

About 10% of the asthmatic population has a severe form of the disease that can require progressively higher doses of corticosteroid drugs to manage the symptoms. Now a new therapeutic approach, described in the December 2005 issue of *Thorax*, may help people whose severe asthma symptoms no longer respond to steroid treatments.

Early research suggested that asthma was a so-called Th2 cytokine disorder involving certain white blood cells known as eosinophils. However, Stephen T. Holgate, a professor in the Infection, Inflammation, and Repair Division of Southampton General Hospital in the United Kingdom, and other researchers noticed that severe asthma was actually associated with neutrophils, another type of white blood cell that is associated with Th1 diseases such as rheumatoid arthritis and psoriasis. These diseases respond well to treatments that block the action of an immune system molecule called tumor necrosis factor–alpha (TNF-α). If severe asthma was truly a Th1 disease, Holgate hypothesized, it stood to reason that it too would respond to a TNF-α blocker.



Asthma attacker? The drug etanercept binds to TNF-α to block its action on the immune system. The drug may be an effective treatment for severe asthma aggravated by factors that affect immunity, such as viruses and air pollution.

To test this idea, Holgate and his colleagues administered the drug etanercept (Enbrel®) to 17 subjects with severe asthma in a 12-week study. Etanercept is a soluble receptor that binds to TNF-α. Treatment was associated with significant improvements in asthma symptoms and lung function, and reduction of bronchial hyperresponsiveness (abnormal sensitivity to agents that narrow the airways) in the 15 patients who completed the regimen.

Some research now suggests that asthma is not a single disease. "Mild and moderate forms of asthma may be disorders primarily characterized by a Th2-type immune response associated with allergen-specific IgE antibodies," Holgate says. "In contrast, severe asthma, which is aggravated by viruses and air pollution, may be a separate Th1-type immune disorder that involves the excess production of TNF-α." This could explain why the use of etanercept in previous studies of mild asthma produced no improvement in symptoms.

Although the improvement in asthma symptoms and airway hyperresponsiveness are impressive, placebo-controlled studies are needed to assess the efficacy of anti-TNF-α therapy. According to Holgate, such studies are now under way in his and other laboratories, and the preliminary results look quite promising. "In twenty-seven years of asthma research, this is the biggest breakthrough that [our research group has] had," he says. **–Michael Szpir**

Wyeth Pharmaceuticals

ehpnet

National Institute of Neurological Disorders and Stroke

More than 600 disorders affect the nervous system, and neurological disorders strike an estimated 50 million Americans annually. The National Institute of Neurological Disorders and Stroke (NINDS) is the NIH institute charged with overseeing research on these conditions. The NINDS website at http://www.ninds.nih.gov/ provides the latest news concerning the institute, its programs, and neurological science in general, as well as a resource on the entire spectrum of neurological diseases.

At the top of the homepage is a Disorder Index of the many neurological conditions that the NINDS addresses. Selecting one of the hundreds of disorders takes visitors to in-depth information about the disorder's symptoms, methods of diagnosis, treatment options, research being done on the disorder, organizations devoted to the disorder, related NINDS publications (including information in Spanish) and additional resources from MedlinePlus.

The site's homepage features the latest news about neurological diseases, with an archive of older items. The homepage also includes a section listing studies that are seeking subjects. Here, visitors can learn more about what clinical trials really are; those who wish to participate in a clinical trial can choose from an extensive list of neurological conditions, from ADHD to Zellweger syndrome, to see what research is in progress or coming up at the NINDS and elsewhere across the country.

Two sections of the homepage allow researchers to find out about funding opportunities. Under the Funding Opportunities header, visitors can retrieve lists of NINDS opportunities either for the last 60 days or all current opportunities. This section also has information on electronic submission of grant applications and answers questions potential grantees may have about new government requirements for submitting grant applications online. Under the Funding Newsletters header, visitors can sign up for the free *NINDS Notes* newsletter, published three times a year, which contains information on grant applications, requests for applications, and studies that need volunteers. The most current newsletter, plus links to previous editions, are available on the site.

The Neuroscience at NIH section of the homepage contains three sections. The Research at NINDS (Intramural) section contains links to information about NINDS faculty, research facilities, events, and training programs such as summer programs and fellowships. The NIH Blueprint section contains an overview of and link to an NIH framework "to enhance cooperative activities among fifteen NIH Institutes and Centers that support research on the nervous system." This section also has links to requests for information and requests for applications related to the blueprint. Finally, the Neuroscience@NIH section contains information about NIH neuroscience faculty, areas of research interest, seminars, interest groups, and postdoctoral openings. **–Erin E. Dooley**

New Guidelines for Pediatric Asthma

More than 6 million U.S. children have asthma, the leading cause of school absenteeism attributable to chronic conditions and the third leading cause of hospitalization among children under age 15. In November 2005, the National Environmental Education & Training Foundation released *Environmental Management of Pediatric Asthma: Guidelines for Healthcare Providers*. Funded by the NIEHS, the peer-reviewed guidance was built on current best practices and includes competencies for managing environmental asthma triggers in pediatric care, an environmental history form for clinicians to use, and intervention guidelines and fliers for specific triggers such as dust mites, cockroaches, and mold spores. Incorporating these guidelines into medical and nursing curricula could give future generations of primary care providers the tools to better manage pediatric asthma.

Own Private Kyoto

Despite producing 24% of all greenhouse gas emissions worldwide, the United States has not signed on to the Kyoto Protocol to reduce greenhouse gases. An analysis in the 17 November 2005 *Nature* shows, however, that as much as one-third of the U.S. population lives in areas that have adopted their own climate change abatement policies. Together, these regions contribute almost half of the U.S. GDP, a slightly larger share of the global GDP than Japan, the world's second largest economy. The authors warn that compliance could be challenging, though, especially since there are currently no mechanisms for enforcement.

Software for Sorting Satellite Images

NASA satellites generate enough data daily to fill 1,500 copies of the *Encyclopedia Britannica*, but satellite data maps often have blank spots where a satellite wasn't able to record data on a particular day. Now statisticians at The Ohio State University have developed new software that can help researchers rapidly process incoming data to produce complete, detailed maps. In an example given by lead statistician Noel Cressie, it could take one person 500 years to fill in the gaps in a map depicting the thickness of the ozone layer, while the same job would take three minutes with the new software. The software also calculates a measure of map precision.

Top to bottom: Banana Stock; NINDS; NASA